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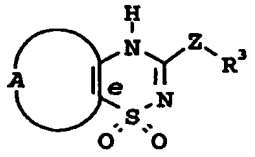
(54) Title: FUSED 1,2,4–THIADIAZINE DERIVATIVES, THEIR PREPARATION AND USE



(I)

(57) Abstract

Fused 1,2,4–thiadiazine derivatives represented by formula (I) wherein A, Z and R^3 are defined in the description, compositions thereof and methods for preparing the compounds are described. The compounds are useful in the treatment of diseases of the central nervous system, the cardiovascular system, the pulmonary system, the gastrointestinal system and the endocrinological system.

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Fused 1,2,4-Thiadiazine Derivatives, their Preparation and Use

FIELD OF THE INVENTION

The present invention relates to fused 1,2,4-thiadiazine derivatives, to methods for their preparation, to compositions comprising the compounds, to the use of these compounds as medicaments and their use in therapy e.g. in the treatment of diseases of the central nervous system, the cardiovascular system, the pulmonary system, the gastrointestinal system and the endocrinological system.

BACKGROUND OF THE INVENTION

Potassium channels play an important role in the physiological and pharmacological control of cellular membrane potential. Amongst the different types of potassium channels are the ATP-sensitive (K_{ATP}-) channels which are regulated by changes in the intracellular concentration of adenosine triphosphate. The K_{ATP}-channels have been found in cells from various tissues such as cardiac cells, pancreatic cells, skeletal muscles, smooth muscles, central neurons and adenohypophysis cells. The channels have been associated with diverse cellular functions for example hormone secretion (insulin from pancreatic beta-cells, growth hormone and prolactin from adenohypophysis cells), vasodilation (in smooth muscle cells), cardiac action potential duration, neurotransmitter release in the central nervous system.

Modulators of the K_{ATP}-channels have been found to be of importance for the treatment of various diseases. Certain sulphonylureas which have been used for the treatment of non-insulin-dependent diabetes mellitus act by stimulating insulin release through an inhibition of the K_{ATP} -channels on pancreatic beta-cells.

The potassium channel openers, which comprise a heterogeneous group of compounds, have been found to be able to relax vascular smooth muscles and have therefore been used for the treatment of hypertension.
In addition, potassium channel openers can be used as bronchodilators in the treatment of asthma and various other diseases.

Furthermore, potassium channel openers have been shown to promote hairgrowth, and have been used for the treatment of baldness.

Potassium channel openers are also able to relax urinary bladder smooth muscle and therefore, can be used for the treatment of urinary incontinence. Potassium channel openers which relax smooth muscle of the uterus can be used for treatment of premature labor.

By acting on potassium channels of the central nervous system these compounds can be used for treatment of various neurological and psychiatric diseases such as Alzheimer, epilepsia and cerebral ischemia.

Further, the compounds are found to be useful in the treatment of benign prostatic hyperplasia, erectile dysfunction and in contraception.

Compounds of the present invention, which inhibit insulin secretion by activating potassium channels of the beta-cell can be used in combination with other compounds which may be used to treat non-insulin dependent diabetes mellitus and insulin dependent diabetes mellitus. Examples of such compounds are insulin, insulin sensitizers, such as thiazolidinediones, insulin secretagogues, such as repaglinide, tolbutamide, glibenclamide and glucagon like peptide (GLP1), inhibitors of α-glucosidases and hepatic enzymes responsible for the biosynthesis of glucose.

Recently, it has been shown that Diazoxide (7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide) and certain 3-(alkylamino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide derivatives inhibit insulin release by an activation of K_{ATP}-channels on pancreatic beta-cells (Pirotte B. et al. *Biochem. Pharmacol,* 47, 1381-1386 (1994); Pirotte B. et al., *J. Med. Chem.*, 36, 3211-3213 (1993). Diazoxide has furthermore been shown to delay the onset of diabetes in BB-rats (Vlahos WD et al. *Metabolism* 40, 39-46 (1991)). In obese zucker rats diazoxide has been shown to decrease insulin secretion and increase insulin receptor binding and consequently improve glucose tolerance and decrease weight gain (Alemzadeh R. et al. Endocrinol. 133, 705-712, 1993). It is expected that compounds which activate K_{ATP}-channels can be used for treatment of diseases characterised by an

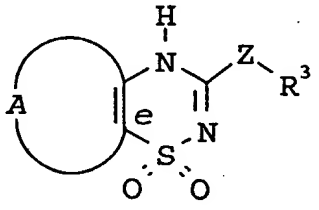
overproduction of insulin and for the treatment and prevention of diabetes.

EP 618 209 discloses a class of pyridothiadiazine derivatives having an alkyl or an alkylamino group in position 3 of the thiadiazine ring. These compounds are claimed to be agonists at the AMPA-glutamate receptor.

In J. Med. Chem. 1980, 23, 575-577 the synthesis of 4(5)-amino-and formylaminoimidazo-5(4) carboxamide and their properties as agents of chemotherapeutic value are described. Especially, the compounds 3-aminoimidazo[4,5-e]-1,2,4-thiadiazine 1,1-dioxide and N-benzoylaminoimidazo[4,5-e]-1,2,4-thiadiazine 1,1-dioxide are shown.

DESCRIPTION OF THE INVENTION

The present invention relates to fused 1,2,4-thiadiazine derivatives of the general formula I:



(I)

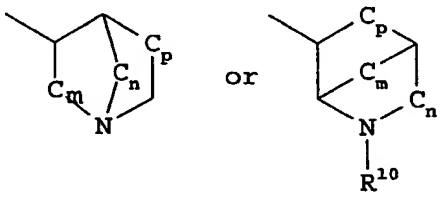
wherein Z is O, S, S(=O), $S(=O)_2$, S(=NR), S(=O)(=NR) or $S(=NR)_2$

wherein R is hydrogen; C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl optionally mono- or polysubstituted with halogen, hydroxy or C_{1-6}-alkoxy; or C_{3-6}-cycloalkyl optionally mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy;

R^3 is C_{3-6}-cycloalkyl or (C_{3-6}-cycloalkyl)C_{1-6}-alkyl the C_{3-6}-cycloalkyl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; a 3-6 membered saturated ring system comprising one or more nitrogen-, oxygen- or sulfur atoms,

optionally being mono- or polysubstituted with halogen, cyano, trifluoromethyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, aryl, arylalkyl, hydroxy, oxo, nitro, amino, C_{1-6}-monoalkyl or dialkylamino; or straight or branched C_{1-18}-alkyl, C_{2-18}-alkenyl or C_{2-18}-alkynyl, each of the groups being optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkylthio, C_{3-6}-cycloalkyl, nitro, amino, C_{1-6}- monoalkyl- or dialkylamino, cyano, oxo, formyl, acyl, carboxy, C_{1-6}-alkoxycarbonyl, carbamoyl, formylamino, or C_{1-6}-alkylcarbonylamino, aryl, aryloxy, arylalkoxy; bicycloalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl, each of the groups being optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, aryloxy, arylalkoxy, nitro, amino, C_{1-6}-monoalkyl- or dialkylamino, cyano, oxo, acyl or C_{1-6}-alkoxycarbonyl;

or R^3 is



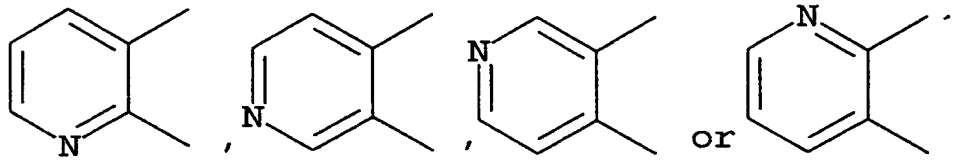
wherein n,m,p independently are 0,1,2,3 and R^{10} is hydrogen; hydroxy; C_{1-6}-alkoxy; C_{3-6}-cycloalkyl optionally mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl optionally mono- or polysubstituted with halogen;

A together with the carbon atoms forming bond *e* of formula I represents a 5 or 6 membered heterocyclic system comprising one or more nitrogen-, oxygen- or sulfur atoms, the heterocyclic systems optionally being mono- or polysubstituted with halogen; C_{1-18}-alkyl; C_{3-6}-cycloalkyl; hydroxy; C_{1-6}-alkoxy; C_{1-6}-alkoxy-C_{1-6}-alkyl; nitro; amino; cyano; cyanomethyl; perhalomethyl; C_{1-6}-monoalkyl- or dialkylamino; sulfamoyl; C_{1-6}-alkylthio; C_{1-6}-alkylsulfonyl; C_{1-6}-alkylsulfinyl; C_{1-6}-alkylcarbonylamino; arylthio, arylsulfinyl, arylsulfonyl, aryl, arylalkyl, aryloxy, the aryl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, perhalomethyl, halogen, hydroxy or C_{1-6}-alkoxy; C_{1-6}-alkoxycarbonyl; C_{1-6}-alkoxycarbonyl-C_{1-6}-alkyl; carbamyl; carbamylmethyl; C_{1-6}-monoalkyl- or dialkylaminocar-

bonyl; C_{1-6}-monoalkyl- or dialkylaminothiocarbonyl; ureido; C_{1-6}-monoalkyl- or dialkylaminocarbonylamino, thiocarbamyl; thioureido; C_{1-6}-monoalkyl- or dialkylaminothiocarbonylamino; C_{1-6}-monoalkyl- or dialkylaminosulfonyl; carboxy; carboxy-C_{1-6}-alkyl; acyl; formyl; or a 5 - 6 membered nitrogen, oxygen or sulfur containing ring, optionally substituted with C_{1-6}-alkyl or phenyl, the phenyl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, perhalomethyl, halogen, hydroxy or C_{1-6}-alkoxy;

or a salt thereof with a pharmaceutically acceptable acid or base,

provided that *A* together with the carbon atoms forming bond *e* of formula I cannot be a pyridine ring selected from



Within its scope the invention includes all optical isomers of compounds of formula I, some of which are optically active, and also their mixtures including racemic mixture thereof.

The scope of the invention also includes all tautomeric forms of the compounds of formula I.

The salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts or optionally alkylated ammonium salts, such as hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, trifluoroacetic, trichloroacetic, oxalic, maleic, pyruvic, malonic, succinic, citric, tartaric, fumaric, mandelic, benzoic, cinnamic, methanesulfonic, ethane sulfonic, picric and the like, and include acids related to the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) and incorporated herein by reference, or lithium, sodium, potassium, magnesium and the like.

The term "C_{1-6}-alkoxy" as used herein, alone or in combination, refers to a straight or branched monovalent substituent comprising a C_{1-6}-alkyl group linked through an ether oxygen having its free valence bond from the ether oxygen and having 1 to 6 carbon atoms e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentoxy.

The term "C_{1-6}-alkylthio" as used herein, alone or in combination, refers to a straight or branched monovalent substituent comprising a lower alkyl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom and having 1 to 6 carbon atoms e.g. methylthio, ethylthio, propylthio, butylthio, pentylthio.

The terms "C_{2-6}-alkenyl" and "C_{2-18}-alkenyl" as used herein refers to an unsaturated hydrocarbon chain having 2-6 or 2-18 carbon atoms and one double bond such as e.g. vinyl, 1-propenyl, allyl, isopropenyl, n-butenyl, n-pentenyl and n-hexenyl.

The term "C_{3-6}-cycloalkyl" as used herein refers to a radical of a saturated cyclic hydrocarbon with the indicated number of carbons such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

The terms "C_{2-6}-alkynyl" and "C_{2-18}-alkynyl" as used herein refers to unsaturated hydrocarbons which contain triple bonds, such as e.g. -C≡CH, -C≡CCH_3, -CH_2C≡CH, -CH_2CH_2C≡CH, -CH(CH_3)C≡CH, and the like.

The term "C_{1-6}-alkoxy-C_{1-6}-alkyl" as used herein refers to a group of 2-12 carbon atoms interrupted by an O such as e.g. CH_2-O-CH_3, CH_2-O-CH_2-CH_3, CH_2-O-CH(CH_3)$_2$ and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine.

The term "perhalomethyl" means trifluoromethyl, trichloromethyl, tribromomethyl or triiodomethyl.

The terms "C_{1-6}-alkyl", "C_{1-12}-alkyl" and "C_{1-18}-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having the indicated number

of carbon atoms such as e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 2-methylbutyl, 3-methylbutyl, 4-methylpentyl, neopentyl, n-hexyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1,2,2-trimethylpropyl and the like. The term "C_{1-18}-alkyl" as used herein also includes secondary C_{3-6}-alkyl and tertiary C_{4-6}-alkyl.

The term "C_{1-6}-monoalkylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with a straight or branched, saturated hydrocarbon chain having the indicated number of carbon atoms such as e.g. methylamino, ethylamino, propylamino, n-butylamino, sec-butylamino, isobutylamino, tert-butylamino, n-pentylamino, 2-methylbutylamino, n-hexylamino, 4-methylpentylamino, neopentylamino, n-hexylamino, 2,2-dimethylpropylamino and the like.

The term "C_{1-6}-dialkylamino" as used herein refers to an amino group wherein the two hydrogen atoms independently are substituted with a straight or branched, saturated hydrocarbon chain having the indicated number of carbon atoms; such as dimethylamino, N-ethyl-N-methylamino, diethylamino, dipropylamino, N-(n-butyl)-N-methylamino, di(n-pentyl)amino, and the like.

The term "acyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-alkyl group linked through a carbonyl group; such as e.g. acetyl, propionyl, butyryl, isobutyryl, pivaloyl, valeryl, and the like.

The term "C_{1-6}-alkoxycarbonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-alkoxy group linked through a carbonyl group; such as e.g. methoxycarbonyl, carbethoxy, propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 3-methylbutoxycarbonyl, n-hexoxycarbonyl and the like.

The term "3-6 membered saturated ring system" as used herein refers to a monovalent substituent comprising a monocyclic saturated system containing one or more hetero atoms selected from nitrogen, oxygen and sulfur and having 3-6 members and having its free valence from a carbon atom, e.g. 2-pyrrolidyl, 4-piperidyl, 3-morpholinyl, 1,4-dioxan-2-yl, 5-oxazolidinyl, 4-isoxazolidinyl, or 2-thiomorpholinyl.

The term "bicycloalkyl" as used herein refers to a monovalent substituent comprising a bicyclic structure made of 6-12 carbon atoms such as e.g. 2-norbornyl, 7-norbornyl, 2-bicyclo[2.2.2]octyl, and 9-bicyclo[3.3.1]nonanyl.

The term "aryl" as used herein refers to phenyl, 1-naphthyl, or 2-naphthyl.

The term "heteroaryl" as used herein, alone or in combination, refers to a monovalent substituent comprising a 5-6 membered monocyclic aromatic system or a 9-10 membered bicyclic aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, e.g. pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine, and purine.

The term "arylalkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with an aromatic carbohydride; such as benzyl, phenethyl, 3-phenylpropyl, 1-naphtylmethyl, 2-(1-naphtyl)ethyl and the like.

The term "aryloxy" as used herein refers to phenoxy, 1-naphthyloxy or 2-naphthyloxy.

The term "arylalkoxy" as used herein refers to a C_{1-6}-alkoxy group substituted with an aromatic carbohydride, such as benzyloxy, phenethoxy, 3-phenylpropoxy, 1-naphthylmethoxy, 2-(1-naphtyl)ethoxy and the like.

The term "C_{1-6}-alkylsulfonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-alkyl group linked through a sulfonyl group such as e.g. methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, sec-butylsulfonyl, isobutylsulfonyl, tert-butylsulfonyl, n-pentylsulfonyl, 2-methylbutylsulfonyl, 3-methylbutylsulfonyl, n-hexylsulfonyl, 4-methylpentylsulfonyl, neopentylsulfonyl, n-hexylsulfonyl and 2,2-dimethylpropylsulfonyl.

The term "C_{1-6}-monoalkylaminosulfonyl" as used herein refers to a monovalent substituent

comprising a C_{1-6}-monoalkylamino group linked through a sulfonyl group such as e.g. methylaminosulfonyl, ethylaminosulfonyl, n-propylaminosulfonyl, isopropylaminosulfonyl, n-butylaminosulfonyl, sec-butylaminosulfonyl, isobutylaminosulfonyl, tert-butylaminosulfonyl, n-pentylaminosulfonyl, 2-methylbutylaminosulfonyl, 3-methylbutylaminosulfonyl, n-hexylaminosulfonyl, 4-methylpentylaminosulfonyl, neopentylaminosulfonyl, n-hexylaminosulfonyl and 2,2-dimethylpropylaminosulfonyl.

The term "C_{1-6}-dialkylaminosulfonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-dialkylamino group linked through a sulfonyl group such as dimethylaminosulfonyl, N-ethyl-N-methylaminosulfonyl, diethylaminosulfonyl, dipropylaminosulfonyl, N-(n-butyl)-N-methylaminosulfonyl, di(n-pentyl)aminosulfonyl, and the like.

The term "C_{1-6}-alkylsulfinyl" as used herein refers to a monovalent substituent comprising a straight or branched C_{1-6}-alkyl group linked through a sulfinyl group (-S(=O)-); such as e.g. methylsulfinyl, ethylsulfinyl, isopropylsulfinyl, butylsulfinyl, pentylsulfinyl, and the like.

The term "C_{1-6}-alkylcarbonylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with an acyl group, such as e.g. acetamido, propionamido, isopropylcarbonylamino, and the like.

The term "(C_{3-6}-cycloalkyl)C_{1-6}-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having 1 to 6 carbon atoms and being monosubstituted with a C_{3-6}-cycloalkyl group, the cycloalkyl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; such as e.g. cyclopropylmethyl, (1-methylcyclopropyl)methyl, 1-(cyclopropyl)ethyl, cyclopentylmethyl, cyclohexylmethyl, and the like.

The term "arylthio" as used herein, alone or in combination, refers to an aryl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom, the aryl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; e.g. phenylthio, (4-methylphenyl)- thio, (2-chlorophenyl)thio, and the like.

The term "arylsulfinyl" as used herein refers to an aryl group linked through a sulfinyl group (-

S(=O)-), the aryl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; such as e.g. phenylsulfinyl, (4-chlorophenyl)sulfinyl, and the like.

The term "arylsulfonyl" as used herein refers to an aryl group linked through a sulfonyl group, the aryl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; such as e.g. phenylsulfonyl, tosyl, and the like.

The term "C_{1-6}-monoalkylaminocarbonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-monoalkylamino group linked through a carbonyl group such as e.g. methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, n-butylaminocarbonyl, sec-butylaminocarbonyl, isobutylaminocarbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, 2-methylbutylaminocarbonyl, 3-methylbutylamino-carbonyl, n-hexylaminocarbonyl, 4-methylpentylaminocarbonyl, neo-pentylaminocarbonyl, n-hexylaminocarbonyl and 2-2-dimethylpropylaminocarbonyl.

The term "C_{1-6}-dialkylaminocarbonyl" as used herein refers to a monovalent substituent comprising a C_{1-6}-dialkylamino group linked through a carbonyl group such as dimethylaminocarbonyl, N-ethyl-N-methylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, N-(n-butyl)-N-methylaminocarbonyl, di(n-pentyl)aminocarbonyl, and the like.

The term "C_{1-6}-monoalkylaminocarbonylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with a C_{1-6}-monoalkylaminocarbonyl group, e.g. methylaminocarbonylamino, ethylaminocarbonylamino, n-propylaminocarbonylamino, isopropylaminocarbonylamino, n-butylaminocarbonylamino, sec-butylaminocarbonylamino, isobutylaminocarbonylamino, tert-butylaminocarbonylamino, and 2-methylbutylaminocarbonylamino.

The term "C_{1-6}-dialkylaminocarbonylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with a C_{1-6}-dialkylaminocarbonyl group, such as dimethylaminocarbonylamino, N-ethyl-N-methylaminocarbonylamino, diethylaminocarbonylamino, dipropylaminocarbonylamino, N-(n-butyl)-N-methylaminocarbonylamino, di(n-pentyl)aminocarbonylamino, and the like.

The term "5- or 6-membered heterocyclic system" as used herein refers to: a monocyclic unsaturated or saturated system containing one, two or three hetero atoms selected from nitrogen, oxygen and sulfur and having 5 members, e.g. pyrrole, furan, thiophene, pyrroline, dihydrofuran, dihydrothiophene, imidazole, imidazoline, pyrazole, pyrazoline, oxazole, thiazole, isoxazole, isothiazole, 1,2,3-oxadiazole, furazan, 1,2,3-triazole, 1,2,3-thiadiazole or 2,1,3-thiadiazole; an aromatic monocyclic system containing two or more nitrogen atoms and having 6 members, e.g. pyrazine, pyrimidine, pyridazine, 1,2,4-triazine, 1,2,3-triazine or tetrazine; a non-aromatic monocyclic system containing one or more hetero atoms selected from nitrogen, oxygen and sulfur and having 6 members, e.g. pyran, thiopyran, piperidine, dioxane, oxazine, isoxazine, dithiane, oxathine, thiazine, piperazine, thiadiazine, dithiazine or oxadiazine.

The term "5- or 6-membered nitrogen, oxygen or sulfur containing ring" as used herein refers to a monovalent substituent comprising a monocyclic unsaturated or saturated system containing one or more nitrogen, oxygen or sulfur atoms and having 5 or 6 members, e.g. pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, pyrrolyl, 2H-pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, morpholino, thiomorpholino, isothiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, 1,3-dioxolanyl, and 1,4-dioxolanyl.

In a preferred embodiment of the invention, *A* together with the thiadiazine ring forms one of the following bicyclic rings: thieno[3,2-e]-1,2,4-thiadiazine, thieno[2,3-e]-1,2,4-thiadiazine or thieno[3,4-e]-1,2,4-thiadiazine.

Preferred compounds of the invention are:

6-Chloro-3-ethylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-propylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-isopropylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-cyclopropylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-(1,2-dimethylpropyl)sulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-isobutylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-cyclobutylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-cyclopentylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Bromo-3-isopropylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Fluoro-3-isopropylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-propylsulfanyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-isopropylsulfanyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-isobutylsulfanyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-cyclopentylsulfanyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-ethylsulfinyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-ethylsulfinimidoyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-ethylsulfonimidoyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-isopropylsulfinimidoyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-ethoxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-propoxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-isopropoxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-cyclopropyloxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-(1,2-dimethylpropoxy) -4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-isobutoxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-cyclobutyloxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-cyclopentyloxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Bromo-3-isopropoxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Fluoro-3-isopropoxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-propoxy-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-isopropoxy-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-isobutoxy-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-cyclopentyloxy-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-cyclopropylmethylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-chloro-3-cyclopropylmethoxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
3-sec-Butylsulfanyl-6-chloro-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-propylsulfinyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-methoxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-propylsulfonimidoyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
5,7-Dichloro-3-methylsulfanyl-4H-thieno[3,4-e]-1,2,4-thiadiazine 1,1-dioxide
7-Bromo-6-chloro-3-methylsulfanyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

7-Bromo-6-chloro-3-methylsulfinyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
7-Bromo-6-chloro-3-methanesulfonyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide
3-Benzylsulfanyl-6-chloro-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-methylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

The compounds of the present invention interact with the potassium channels and hence act as openers or blockers of the ATP-regulated potassium channels, which make them useful in the treatment of various diseases of the cardiovascular system, e.g. cerebral ischemia, hypertension, ischemic heart diseases, angina pectoris and coronary heart diseases; the pulmonary system; the gastrointestinal system; the central nervous system and the endocrinological system.

Since some K_{ATP}-openers are able to antagonize vasospasms in basilar or cerebral arteries the compounds of the present invention can be used for the treatment of vasospastic disorders such as subarachnoid haemorrhage and migraine.

The compounds of the present invention may also be used for the treatment of diseases associated with decreased skeletal muscle blood flow such as Raynauds disease and intermittent claudication.

Further, the compounds of the invention may be used for the treatment of chronic airway diseases, including asthma, and for treatment of detrusor muscle instability secondary to bladder outflow obstruction and therefore for kidney stones by aiding their passage along the urethra.

The present compounds could also be used for treatment of conditions associated with disturbances in gastrointestinal mobility such as irritable bowel syndrome. Additionally these compounds can be used for the treatment of premature labour and dysmenorrhea.

Potassium channel openers hyperpolarize neurons and inhibit neurotransmitter release and it is expected that such compounds can be used for the treatment of various diseases of the central nervous system, e.g. epilepsia, ischemia and neurodegenerative diseases, and for the management of pain.

Further, potassium channel openers promote hairgrowth, therefore, the compounds of the present invention can be used for the treatment of baldness.

Potassium channel openers also relax urinary bladder smooth muscle, thus, the compounds of the present invention can be used for the treatment of urinary incontinence.

In diseases such as nesidioblastosis and insulinoma in which a hypersecretion of insulin causes severe hypoglycemia the compounds of the present invention can be used to reduce insulin secretion. In obesity hyperinsulinemia and insulin resistance is very frequently encountered. This condition could lead to the development of noninsulin dependent diabetes (NIDDM). It is expected that potassium channel openers, and hence the compounds of the present invention, can be used for reducing the hyperinsulinemia and thereby prevent diabetes and reduce obesity. In overt NIDDM treatment of hyperinsulinemia with potassium channel openers, and hence the present compounds, can be of benefit in restoring glucose sensitivity and normal insulin secretions.

In early cases of insulin dependent diabetes (IDDM) or in prediabetic cases, potassium channel openers and hence the present compounds can be used to induce pancreatic cell rest which may prevent the progression of the autoimmune disease.

The potassium channel openers of the present invention can be administered in combination with an immunosuppressant or with an agent like nicotinamide, which will reduce autoimmune degeneration of beta-cells.

Combining beta-cell rest with a treatment protecting the beta-cells against cytokine mediated beta-cell impairment/cytotoxicity is another aspect of this invention. Insulin requiring or Type 1 diabetes (IDDM) as well as late onset IDDM (also known as type 1.5. e.g. non-insulin-requiring Type 2 (NIIDM) patients with autoreactivity against beta-cell epitopes that later turns insulin requiring) have circulating autoreactive monocytes/lymphocytes that homes to the islets/beta-cells and releases their cytokines. Some of these cytokines (e.g. interleukin-1b (IL-1b) , tumour necrosis factor a (TNFa) and interferon g (IFNg)) are specifically toxic to the beta-cells, e.g. through the induction of

nitric oxide (NO) and other free radicals. Inhibition of this cytotoxicity, e.g. by co-administring nicotinamide (NA), a derivative hereof or other cytokine protective compounds to the prediabetic/diabetic patients treated with the PCO compound is an example of this aspect. Nicotinamide belongs to the B-vitamin family and is derived from nicotinic acid by amidation of the carboxyl group. It processes none of nicotine's pharmacological properties. NA is converted into NAD+, which acts as a coenzyme for proteins involved in tissue respiration. NA has been proposed to influence several of the putative intracellular molecular events following immune attack on the beta-cells. Animal experiments and early non-blinded experiments in humans have indicated a protective role of this compound against IDDM as well as in cytokine/immune mediated beta-cell destruction.

Yet another aspect of this application concerns the use of a PCO compound alone or in combination with the inhibitor of cytokine/immune mediated beta-cell impairment , in transplantation, e.g. islet transplantation into diabetes patients. The use of one or both of these treatments may reduce the risk of rejection of the transplanted islets/beta-cells/engineered beta-cells/pancreas.

Compounds of the present invention which act as blockers of K_{ATP} -channels can be used for the treatment of NIDDM.

Preferably, the compounds of the present invention may be used for treatment or prevention of diseases of the endocrinological system such as hyperinsulinaemia and diabetes.

Accordingly, in another aspect the invention relates to a compound of the general formula I or a pharmaceutically acceptable acid addition salt thereof for use as a therapeutically acceptable substance, preferably for use as a therapeutically acceptable substance in the treatment of hyperinsulinaemia and treatment or prevention of diabetes.

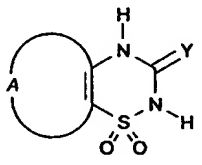
Furthermore, the invention also relates to the use of the inventive compounds of formula I as medicaments useful for treating hyperinsulinaemia and treating or preventing diabetes

Optionally, the pharmaceutical composition of the invention may comprise a com-

pound of formula I combined with one or more other pharmacologically active compounds, e.g. an antidiabetic or other pharmacologically active material, including compounds for the treatment and/or prophylaxis of insulin resistance and diseases wherein insulin resistance is the pathophysiological mechanism. Suitable antidiabetics comprise insulin as well as orally active hypoglycaemic agents such as sulphonylureas, e.g. glibenclamide and glipizide; biguanides, e.g. metformin; benzoic acid derivatives, e.g. repaglinide;and thiazolidinediones, e.g. troglitazone and ciglitazone.

In yet another aspect, the present invention relates to methods of preparing the above mentioned compounds. The methods comprises:

a) reacting a compound of formula II:



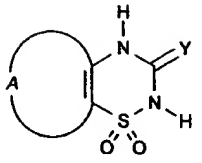
(II)

wherein Y is O or S and A is as defined above with a compound of formula III

$$R^3\text{-}X \qquad \text{(III)}$$

wherein R^3 is as defined above and X is a leaving group such as halogen or sulfate, preferentially chloro, bromo or iodo to form a compound of the general formula I wherein Z is O or S. The reaction may be carried out in a suitable solvent and in the presence of a base, or

b) reacting a compound of formula II:



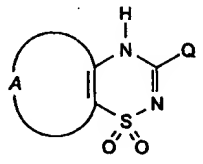
(II)

wherein Y is O and A is as defined above with a compound of formula IV

$$R'R''CN_2 \qquad (IV)$$

wherein R' and R" together as two substituents on methyl form a group R'R"CH meeting the criteria defined above for R^3, to form a compound of the general formula I wherein Z is O and R^3 is R'R"CH, or

c) reacting a compound of formula V:



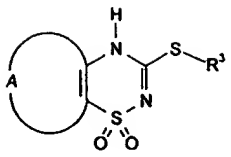
(V)

wherein Q is a leaving group such as halogen, preferentially chloro, bromo, iodo; amino, trimethylamino, imidazol-1-yl, methylsulfanyl, methylsulfinyl or methylsulfonyl with a compound of formula VI:

$$R^3YH \qquad (VI)$$

wherein R^3 is as defined above and Y is O or S to form a compound of the general formula I wherein Z is O or S. The reaction may be carried out in a suitable solvent and in the presence of a base, or

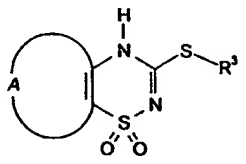
d) reacting a compound of formula VII:



(VII)

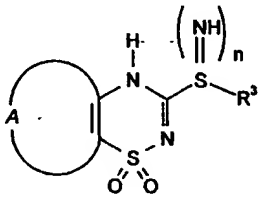
wherein A and R^3 are as defined above with an oxidizing agent to form a compound of the general formula I wherein Z is S(=O) or $S(=O)_2$, or

e) reacting a compound of formula VII:



(VII)

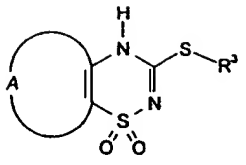
wherein A and R^3 are as defined above with an aminating agent according to known procedures, see e.g. P.D. Kennenwell, J.B. Taylor, Chem.Soc.Rev. (1980) 477-498 and P.D. Kennenwell, J.B. Taylor, Chem.Soc.Rev. (1975) 189-209, to form a compound of the general formula VIII



(VIII)

wherein n is 1 or 2, or

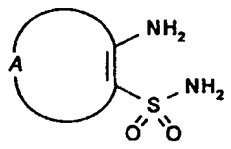
f) reacting a compound of formula VII:



(VII)

wherein A and R^3 are as defined above with an aminating agent and subsequently an oxidizing agent, or vice versa, according to known procedures, see e.g. P.D. Kennenwell, J.B. Taylor, Chem.Soc.Rev. (1980) 477-498 and P.D. Kennenwell, J.B. Taylor, Chem.Soc.Rev. (1975) 189-209, to form a compound of the general formula I wherein Z is S(=O)(=NR), or

g) reacting a compound of formula IX

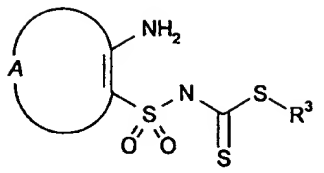


(IX)

wherein A is as defined above with CS_2 in the presence of a base to give the corresponding sulfonylimino carbodithioate which in turn is treated with an alkylating agent of formula III

$$R^3\text{-}X \qquad \text{(III)}$$

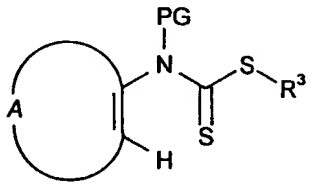
wherein R^3 is as defined above and X is a leaving group such as halogen or sulfate, preferentially chloro, bromo or iodo to form a compound of formula X



(X)

which by ring-closure, e.g. by treatment with phosgene in a suitable solvent, forms a compound of the general formula I, or

h) reacting a compound of formula XI



(XI)

wherein A and R^3 are as defined above and PG is a protecting group, e.g. substituted benzyl, with chlorosulfonyl isocyanate (Cl-SO_2-NCO) and subsequent ring closure followed by removal of the protecting group to form a compound of formula I.

The starting materials are either known compounds or compounds which may be prepared in analogy with the preparation of known compounds or in analogy with known methods as described by e.g. Huang B.-S., et al., J. Med. Chem., 23, 575-7 (1980), Ofitserov V. I. et al., Khim. Geterotsikl. Soedin., 1119-22 (russ.) (1976), Topliss J. G., U.S. 3,641,017 (1972), Kotovskaya S. K. et al., Khim.-Farm. Zh., 13, 54-57 (russ.) (1979), Meyer R. F., J. Heterocycl. Chem., 6, 407-408 (1969), Hattori M., Yoneda M., Goto M., Bull. Chem. Soc. Jap., 46, 1890-1 (1973), Williams T.R. and Cram D.J., J. Org. Chem., 38, 20-26 (1973), T. Iwakawa, H. Tamura, Y. Hayase, Chem.Pharm.Bull. 38(4), 1075-6 (1990), F.E. Nielsen, H.C. Hansen, J.B. Hansen, T.M. Tagmose, PCT Int. Appl. WO 97 / 26265, M.E. Arranz, S. Vega, Heterocycles 45, 1767-1774 (1997).

PHARMACOLOGICAL METHODS

The ability of the compounds to interact with potassium channels can be determined by various methods. When patch-clamp techniques (Hamill O.P., Marty A., Neher E., Sakmann B. and Sigworth F.J., *Plügers Arch.*, 391, 85-100 (1981)) are used the ionic current through a single channel of a cell can be recorded.

The activity of the compounds as potassium channel openers can also be measured as relaxation of rat aorta rings according to the following procedure:

A section of rat thoracic aorta between the aortic arch and the diaphragm was dissected out and mounted as ring preparations as described by Taylor P.D. et al , *Brit. J. Pharmacol*, 111, 42-48 (1994).

After a 45 min. equilibration period under a tension of 2 g, the preparations were contracted to achieve 80% of the maximum response using the required concentration of phenylephrine. When the phenylephrine response reached a plateau, potential vasodilatory agents were added cumulatively to the bath in small volumes using half log molar increments at 2 min intervals. Relaxation was expressed at the percentage of the contracted tension. The potency of a compound was expressed as the concentration required to evoke a 50% relaxation of the tissue.

In the pancreatic b-cell the opening of the K_{ATP}-channels can be determined by measuring the subsequent change in the concentration of cytoplasmic free Ca^{2+} concentration according to the method of Arkhammar P. et al. , *J. Biol. Chem.*, 262, 5448-5454 (1987).

$^{86}Rb^+$ efflux from a ß-cell line

The RIN 5F cell line was grown in RPMI 1640 with Glutamax I, supplemented with 10 % foetal calf serum (from GibcoBRL, Scotland, UK) and maintained in an atmosphere of 5 % CO_2 / 95 % air at 37°C. The cells were detached with a Trypsin-EDTA solution (from GibcoBRL, Scotland, UK), resuspended in medium, added 1 mCi/ml $^{86}Rb^+$ and replated into microtiter plates (96 well cluster 3596, sterile, from Costar Corporation, MA, USA) at a density of 50000 cells/well in 100 µl/well, and grown 24 hours before use in assay.

The plates were washed 4 times with Ringer buffer (150 mM NaCl, 10 mM Hepes, 3.0 mM KCl, 1.0 mM $CaCl_2$, 20 mM Sucrose, pH 7.1). Eighty µl Ringer buffer and 1 µl control- or test compound dissolved in DMSO was added. After incubation 1 h at room temperature with a lid, 50 µl of the supernatant was transferred to PicoPlates (Packard Instrument Company, CT, USA) and 100 µl MicroScint40 (Packard Instrument Company, CT, USA) added. The plates were counted in TopCount (Packard Instrument Company, CT, USA) for 1 min/well at the ^{32}P program.

The calculation of EC_{50} and E_{max} was done by SlideWrite (Advanced Graphics Software, Inc., CA, USA) using a four parameter logistic curve: $y = (a-d)/(1+(x/c)^b)+d$, where a = the activity estimated at concentration zero, b = a slope factor, c = the concentration at the middle of the curve and, d = the activity estimated at infinite concentration. EC_{50} = c and E_{max} = d, when the curve is turned of at infinite concentrations.

The compounds according to the invention are effective over a wide dose range. In general satisfactory results are obtained with dosages from about 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, per day. A most preferable dosage is about 1 mg to about 100 mg per day. The exact dosage will depend upon the mode of administration, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral or parenteral e.g. rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal, the oral route being preferred.

Typical compositions include a compound of formula I or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used.

For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycol's, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

Generally, the compounds are dispensed in unit form comprising from about 1 to about 100 mg in a pharmaceutically acceptable carrier per unit dosage.

A typical tablet, appropriate for use in this method, may be prepared by conventional tabletting techniques and contains:

Active compound	5.0 mg
Lactosum	67.8 mg Ph.Eur.
Avicel®	31.4 mg
Amberlite®	1.0 mg
Magnesii stearas	0.25 mg Ph.Eur.

EXAMPLES

The process of preparing the compounds of formula I is further illustrated in the following examples which, however, are not to be construed as limiting.

EXAMPLE 1

6-Chloro-3-isopropoxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

A solution of 6-chloro-2,3-dihydro-3-oxo-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide potassium salt (0.50 g) and 1 ml of 2-iodopropane was heated at 50 °C for 23 h. The solvent was removed in vacuum and the residue stirred with 10 ml of water and pH was adjusted to 12 by addition of 4M NaOH. The mixture was filtered and the filtrate was adjusted to pH 1 by addition of 4M HCl to give a voluminous precipitate. The mixture was stirred with 5 ml of water and filtered. The filter cake was rinsed rinsed with water and dried to give a beige powder. Recrystallization from ethyl acetate gave 0.11 g of the title compound as pale needles, mp 194 - 195 °C; ^{1}H-NMR (d_6-DMSO), δ (ppm): 12.65 (br, 1H), 6.94 (s, 1H), 5.10 (heptet, 1H), 1.32 (d, 6H).

EXAMPLE 2

6-Chloro-3-cyclopentyloxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

The title compound was prepared from 6-chloro-2,3-dihydro-3-oxo-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide potassium salt and bromocyclopentane by a procedure analogous

to the procedure described in example 1; mp 207-208 °C (dec.); ^{1}H-NMR (d_6-DMSO), δ (ppm): 12.6 (br, 1H), 6.96 (s, 1H), 5.30 (m, 1H), 2.08 - 1.5 (m, 8H).

EXAMPLE 3

6-Chloro-3-cyclopropylmethylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

a) 6-Chloro-2,3-dihydro-3-thioxo-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

The title compound was prepared by thionation of 6-chloro-2,3-dihydro-3-oxo-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide with phosphorous pentasulfide in pyridine in analogy with e.g. Di Bella et al., Farmaco Ed. Sci., 27, 990-998 (1972). The impure crude product with mp 184 °C (dec.) was used for further reactions; IR (KBr), ν (cm^{-1}): 1578, 1557, 1334, 1142.

b) 6-Chloro-3-cyclopropylmethylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

A mixture of 6-chloro-2,3-dihydro-3-thioxo-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide (0.25 g), sodium bicarbonate (84 mg) and cyclopropylmethyl bromide (96 µl) in 1 ml of dry DMF was stirred at 65 °C overnight. The solvent was removed and the residue was triturated with 5 ml of water and filtered. The filter cake was washed with water and dried to give 0.23 g of a brown solid. The solid was extracted with 10 ml of hot ethylacetate-heptane 2:1. The extract was diluted with 2 ml of methanol and treated with charcoal, filtered through a pad of celite and silica gel and evaporated. The residue was triturated three times with 0.5 ml of ethylacetate-heptane 1:1 and dried to give the title compound as pale crystals; mp 232 - 233 °C; ^{1}H-NMR (d_6-DMSO), δ (ppm): 13.1 (br, 1H), 7.02 (s, 1H), 3.10 (d, 2H), 1.25-1.08 (m, 1H), 0.68 - 0.28 (m, 4H).

EXAMPLE 4

6-Chloro-3-ethylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

The title compound was prepared from 6-chloro-2,3-dihydro-3-thioxo-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide and bromoethane by a procedure analogous to the procedure described in example 3b; mp 221-222°C; ^{1}H-NMR (d_6-DMSO), δ (ppm): 13.15 (br, 1H), 7.01 (s, 1H), 3.10 (q, 2H), 1.32 (t, 3H).

EXAMPLE 5

6-Chloro-3-isopropylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

The title compound was prepared from 6-chloro-2,3-dihydro-3-thioxo-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide and 2-bromopropane by a procedure analogous to the procedure described in example 3b; mp 222 - 224 °C; ^{1}H-NMR (d_6-DMSO), δ (ppm): 13.1 (br, NH), 7.00 (s, 1H), 3.80 (heptet, 1H), 1.39 (d, 6H).

EXAMPLE 6

6-Chloro-3-propylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

The title compound was prepared from 6-chloro-2,3-dihydro-3-thioxo-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide and 3-bromopropane by a procedure analogous to the procedure described in example 3b; mp 191 - 194 °C; ^{1}H-NMR (d_6-DMSO), δ (ppm): 13.1 (br, NH), 7.00 (s, 1H), 3.08 (t, 2H), 1.69 (sextet, 2H), 0.98 (t, 3H).

EXAMPLE 7

6-Chloro-3-cyclopentylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1 dioxide

The title compound was prepared from 6-chloro-2,3-dihydro-3-thioxo-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide and bromocyclopentane by a procedure analogous to the procedure described in example 3b; mp 227 - 229 °C; ^{1}H-NMR (d_6-DMSO), δ (ppm): 13.1 (br, NH), 7.00 (s, 1H), 3.96 - 3.79 (m, 1H), 2.30 - 2.05 (m, 2H), 1.82 - 1.48 (m, 6H).

EXAMPLE 8

3-sec-Butylsulfanyl-6-chloro-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

The title compound was prepared from 6-chloro-2,3-dihydro-3-thioxo-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide and 2-bromobutane by a procedure analogous to the procedure described in example 3b; mp 132 - 134 °C; ^{1}H-NMR (d_6-DMSO), δ (ppm): 13.1 (br, NH), 7.01 (s, 1H), 3.70 (sextet, 1H), 1.70 (pentet, 2H), 1.39 (d, 3H), 0.97 (t, 3H).

EXAMPLE 9

6-Chloro-3-isobutylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide The title compound was prepared from 6-chloro-2,3-dihydro-3-thioxo-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide and 1-bromo-2-methylpropane by a procedure analogous to the procedure described in example 3b; mp 233-35 °C; ^{1}H-NMR (d_6-DMSO), δ (ppm): 13.15 (br, NH), 7.00 (s, 1H), 3.03 (d, 2H), 2.05 - 1.82 (m, 1H), 0.99 (d, 6H).

EXAMPLE 10

6-Chloro-3-propylsulfinyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

Oxone ($KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$; 0.77 g) was added over 10 min. to a stirred solution of 6-chloro-3-propylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide (0.5 g) in a mixture of methanol (35 ml) and water (10 ml) at room temperature. After 1.5 h the reaction mixture was filtered. The filter cake was washed with water and dried to yield 0.50 g of crude product. an additional crop of crystals, 0.08 g, precipitated from the filtrate when the washing water was added. The solid products were combined and triturated with 20 ml of water. The insoluble material was collected by filtration, washed with water and dried to give 0.24 g of the title compound; mp 190 - 192 °C; ^{1}H-NMR (d_6-DMSO), δ (ppm): 7.34 (s, 1H), 7 - 6 (br, NH), 3.36 - 3.02 (m, 2H), 1.97 - 1.42 (m, double set, 2H), 1.00 (t, 3H); IR (KBr) ν (cm^{-1}): 3145, 1603, 1518, 1318, 1177, 1065, 1032, 1024, 820, 780; MS: m/e = 312 (M^+), 270, 254, 236, 221, 205, 196, 190, 173, 163, 157, 145, 130, 113, 109, 87, 84, 69, 52, 43.

The filtrate was processed further as described in example 11 below.

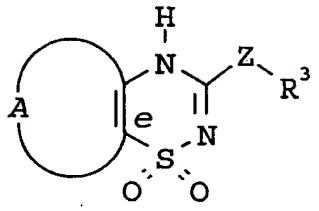
EXAMPLE 11

6-Chloro-3-methoxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

To the filtrate described in example 10 was added an additional amount (0.30 g) of oxone, and the resulting mixture was stirred overnight at room temperature. The reaction mixture was then filtered and the filter cake was dried to give 0.66 g of the title compound; mp 238 - 244 °C; ^{1}H-NMR (d_6-DMSO), δ (ppm): 12.71 (br s, 1H), 6.98 (s, 1H), 3.90 (s, 3H); IR (KBr), ν (cm^{-1}): 3589, 3521, 3204, 3097, 2940, 2859, 2817, 1618, 1582, 1525, 1456, 1391, 1318, 1293, 1161; MS: m/e = 252 (M^+), 188, 173, 131, 69, 52.

CLAIMS

1. A compound of the general formula I:



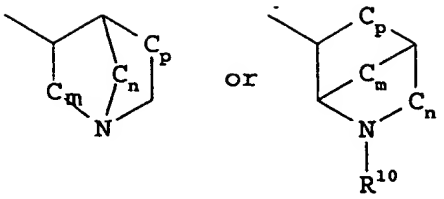
(I)

wherein Z is O, S, S(=O), $S(=O)_2$, S(=NR), S(=O)(=NR) or $S(=NR)_2$

wherein R is hydrogen; C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl optionally mono- or polysubstituted with halogen, hydroxy or C_{1-6}-alkoxy; or C_{3-6}-cycloalkyl optionally mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy;

R^3 is C_{3-6}-cycloalkyl or (C_{3-6}-cycloalkyl)C_{1-6}-alkyl the C_{3-6}-cycloalkyl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; a 3-6 membered saturated ring system comprising one or more nitrogen-, oxygen- or sulfur atoms, optionally being mono- or polysubstituted with halogen, cyano, trifluoromethyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, aryl, arylalkyl, hydroxy, oxo, nitro, amino, C_{1-6}-monoalkyl or dialkylamino; or straight or branched C_{1-18}-alkyl, C_{2-18}-alkenyl or C_{2-18}-alkynyl, each of the groups being optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkylthio, C_{3-6}-cycloalkyl, nitro, amino, C_{1-6}- monoalkyl- or dialkylamino, cyano, oxo, formyl, acyl, carboxy, C_{1-6}-alkoxycarbonyl, carbamoyl, formylamino, or C_{1-6}-alkylcarbonylamino, aryl, aryloxy, arylalkoxy, the aryl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, perhalomethyl, halogen, hydroxy or C_{1-6}-alkoxy; bicycloalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl, each of the groups being optionally mono- or polysubstituted with halogen, hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, aryloxy, arylalkoxy, nitro, amino, C_{1-6}-monoalkyl- or dialkylamino, cyano, oxo, acyl or C_{1-6}-alkoxycarbonyl;

or R^3 is



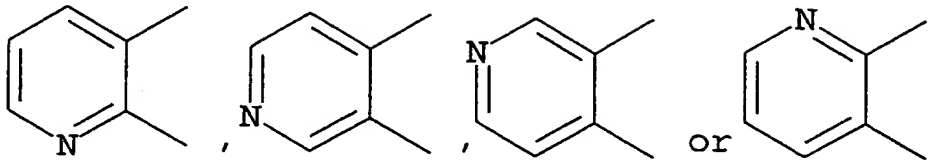
wherein n,m,p independently are 0,1,2,3 and R^{10} is hydrogen; hydroxy; C_{1-6}-alkoxy; C_{3-6}-cycloalkyl optionally mono- or polysubstituted with C_{1-6}-alkyl, halogen, hydroxy or C_{1-6}-alkoxy; C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl optionally mono- or polysubstituted with halogen;

A together with the carbon atoms forming bond *e* of formula I represents a 5 or 6 membered heterocyclic system comprising one or more nitrogen-, oxygen- or sulfur atoms, the heterocyclic systems optionally being mono- or polysubstituted with halogen; C_{1-18}-alkyl; C_{3-6}-cycloalkyl; hydroxy; C_{1-6}-alkoxy; C_{1-6}-alkoxy-C_{1-6}-alkyl; nitro; amino; cyano; cyanomethyl; perhalomethyl; C_{1-6}-monoalkyl- or dialkylamino; sulfamoyl; C_{1-6}-alkylthio; C_{1-6}-alkylsulfonyl; C_{1-6}-alkylsulfinyl; C_{1-6}-alkylcarbonylamino; arylthio, arylsulfinyl, arylsulfonyl, aryl, arylalkyl, aryloxy, the aryl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, perhalomethyl, halogen, hydroxy or C_{1-6}-alkoxy; C_{1-6}-alkoxycarbonyl; C_{1-6}-alkoxycarbonyl-C_{1-6}-alkyl; carbamyl; carbamylmethyl; C_{1-6}-monoalkyl- or dialkylaminocarbonyl; C_{1-6}-monoalkyl- or dialkylaminothiocarbonyl; ureido; C_{1-6}-monoalkyl- or dialkylaminocarbonylamino, thiocarbamyl; thioureido; C_{1-6}-monoalkyl- or dialkylaminothiocarbonylamino; C_{1-6}-monoalkyl- or dialkylaminosulfonyl; carboxy; carboxy-C_{1-6}-alkyl; acyl; formyl; or a 5 - 6 membered nitrogen, oxygen or sulfur containing ring, optionally substituted with C_{1-6}-alkyl or phenyl, the phenyl group optionally being mono- or polysubstituted with C_{1-6}-alkyl, perhalomethyl, halogen, hydroxy or C_{1-6}-alkoxy;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form,

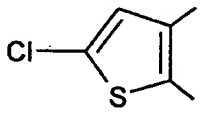
provided that *A* together with the carbon atoms forming bond *e* of formula I cannot be a

pyridine ring selected from



2. A compound according to claim 1, wherein A together with the carbon atoms forming bond e of formula I represents a thiophene ring.

3. A compound according to anyone of the preceding claims wherein *A* together with the carbon atoms forming bond *e* of formula I forms a thiophene ring substituted with chloro according to formula 1A:



(1A)

4. A compound according to anyone of the preceding claims wherein Z is O or S.

5. A compound according to anyone of the preceding claims wherein R^3 is C_{3-6}-cycloalkyl, (C_{3-6}-cycloalkyl)C_{1-6}-alkyl or straight or branched C_{1-18} -alkyl.

6. A compound selected from the following:

6-Chloro-3-ethylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-propylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-isopropylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-cyclopropylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide
6-Chloro-3-(1,2-dimethylpropyl)sulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-isobutylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-cyclobutylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-cyclopentylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Bromo-3-isopropylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Fluoro-3-isopropylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-propylsulfanyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-isopropylsulfanyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-isobutylsulfanyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-cyclopentylsulfanyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-ethylsulfinyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-ethylsulfinimidoyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-ethylsulfonimidoyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-isopropylsulfinimidoyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-ethoxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-propoxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-isopropoxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-cyclopropyloxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-(1,2-dimethylpropoxy) -4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-isobutoxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-cyclobutyloxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-cyclopentyloxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Bromo-3-isopropoxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Fluoro-3-isopropoxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-propoxy-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-isopropoxy-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-isobutoxy-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-cyclopentyloxy-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

6-chloro-3-cyclopropylmethylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-chloro-3-cyclopropylmethoxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

3-sec-Butylsulfanyl-6-chloro-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-propylsulfinyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-methoxy-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-propylsulfonimidoyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

5,7-Dichloro-3-methylsulfanyl-4H-thieno[3,4-e]-1,2,4-thiadiazine 1,1-dioxide

7-Bromo-6-chloro-3-methylsulfanyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

7-Bromo-6-chloro-3-methylsulfinyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

7-Bromo-6-chloro-3-methanesulfonyl-4H-thieno[2,3-e]-1,2,4-thiadiazine 1,1-dioxide

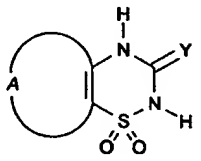
3-Benzylsulfanyl-6-chloro-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

6-Chloro-3-methylsulfanyl-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide

7. Compounds according to any one of the preceding claims which acts as openers of the K_{ATP}-regulated potassium channels.

8. A method of preparing a compound of formula I, characterized in

a) reacting a compound of formula II:



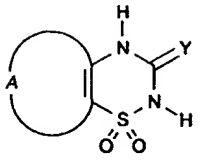
(II)

wherein Y is O or S and A is as defined above with a compound of formula III

$$R^3\text{-}X \qquad \text{(III)}$$

in the presence of a base, wherein R^3 is as defined above and X is a leaving group selected from chloro, bromo or iodo to form a compound of the general formula I wherein Z is O or S, or

b) reacting a compound of formula II:



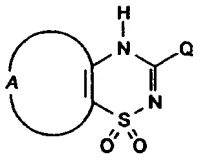
(II)

wherein Y is O and A is as defined above with a diazo compound of formula IV

$$R'R''CN_2 \qquad (IV)$$

wherein R' and R'' together as two substituents on methyl form a group R'R''CH meeting the criteria defined above for R^3, to form a compound of the general formula I wherein Z is O and R^3 is R'R''CH, or

c) reacting a compound of formula V:



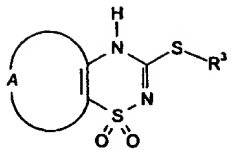
(V)

wherein Q is a leaving group selected from chloro, bromo, iodo, amino, trimethylamino, imidazol-1-yl, methylsulfanyl, methylsulfinyl or methylsulfonyl with a compound of formula VI:

$$R^3YH \qquad (VI)$$

in the presence of a base, wherein R^3 is as defined above and Y is O or S to form a compound of the general formula I wherein Z is O or S, or

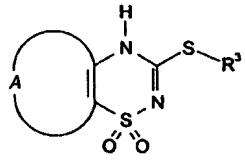
d) reacting a compound of formula VII:



(VII)

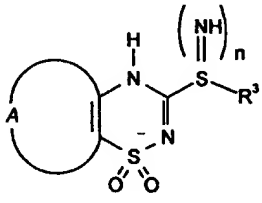
wherein A and R^3 are as defined above with an oxidizing agent to form a compound of the general formula I wherein Z is S(=O) or $S(=O)_2$, or

e) reacting a compound of formula VII:



(VII)

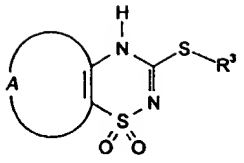
wherein A and R^3 are as defined above with an aminating agent to form a compound of the general formula VIII



(VIII)

wherein n is 1 or 2, or

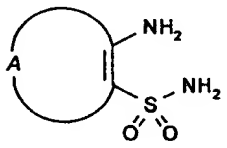
f) reacting a compound of formula VII:



(VII)

wherein A and R^3 are as defined above with an aminating agent and subsequently an oxidizing agent, or vice versa, to form a compound of the general formula I wherein Z is S(=O)(=NR), or

g) reacting a compound of formula IX

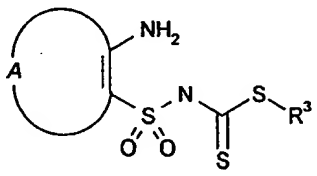


(IX)

wherein A is as defined above with CS_2 in the presence of a base to give the corresponding sulfonylimino carbodithioate which in turn is treated with an alkylating agent of formula III

$$R^3\text{-}X \qquad \text{(III)}$$

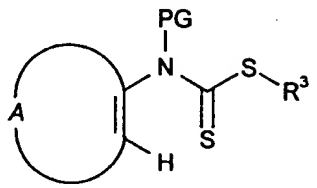
wherein R^3 is as defined above and X is a leaving group selected from sulfate, chloro, bromo or iodo to form a compound of formula X



(X)

which by ring-closure, e.g. by treatment with phosgene in a solvent, forms a compound of the general formula I, or

h) reacting a compound of formula XI



(XI)

wherein A and R^3 are as defined above and PG is a protecting group, selected from substituted benzyl, with chlorosulfonyl isocyanate (Cl-SO_2-N=C=O) and subsequent ring closure followed by removal of the protecting group to form a compound of formula I.

9. A pharmaceutical composition comprising a compound according to any of the claim 1 - 6 or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

10. A pharmaceutical composition for use in the treatment of diseases of the endocrinological system such as hyperinsulinaemia and diabetes comprising a compound according to any of the claims 1 - 6 or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

11. The pharmaceutical composition according to claim 9 or 10 in the form of an oral dosage unit or parenteral dosage unit.

12. A pharmaceutical composition according to claim 9 or 10 wherein said compound is administered as a dose in a range from about 0.05 to 1000, preferably from about 0.1 to

500 and especially in the range from 50 to 200 mg per day.

13. A compound according to any one of the claims 1 - 6 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for therapeutical use.

14. A compound according to any one of the claims 1 - 6 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for therapeutical use in the treatment or prevention of diseases of the endocrinological system, such as hyperinsulinaemia and diabetes.

15. The use of a compound according to any one of the claims 1 - 6 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form as a medicament.

16. The use of a compound according to any of the claims 1 - 6 for preparing a medicament.

17. The use of a compound according to any one of the claims 1 - 6 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of a medicament for the treatment or prevention of diseases of the endocrinological system, such as hyperinsulinaemia and diabetes.

18. A method of treating or preventing diseases of the endocrinological system, such as hyperinsulinaemia and diabetes in a subject in need thereof comprising administering an effective amount of a compound according to any of the claims 1 - 6 to said subject.

19. A process for the manufacture of a medicament, particular to be used in the treatment or prevention of diseases of the endocrinological system, such as

hyperinsulinaemia and diabetes which process comprising bringing a compound of formula I according to any of the claims 1 - 6 or a pharmaceutically acceptable salt thereof into a galenic dosage form.

20. Any novel feature or combination of features as described herein.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 98/00545

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 513/04, A61K 31/54 // (C07D 513/04, 285:00, 333:00)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 9903861 A1 (NOVO NORDISK A/S), 28 January 1999 (28.01.99), page 22, line 6 - page 23, line 16, the claims --	1-20
X	WO 9726265 A1 (NOVO NORDISK A/S), 24 July 1997 (24.07.97), page 21, line 1 - line 12; page 30, line 30, the claims --	1-20
X	J. Med. Chem., Volume 23, No 5, 1980, Bao-Shan Huang et al, "Synthesis and Properties of the Sulfonyl Analogues of 4(5)-Aminoimidazole-5(4)-carboxamide, 4(5)-(Formylamino)imidazole-5(4)-carboxamide, Guanine, and Xanthinel", page 575 - page 577, page 575, Scheme I --	1-6,8,20

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 March 1999	12 -04- 1999
Name and mailing address of the ISA/ Swedish Patent Offic Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 98/00545

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3641017 A (JOHN G. TOPLISS), 8 February 1972 (08.02.72) -- --------	1-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 98/00545

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 15,18
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 15,18 relate to methods of treatment of the human or animal body by surgery or by therapy. See PCT, Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/03/99

International application No.
PCT/DK 98/00545

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9903861 A1	28/01/99	NONE	
WO 9726265 A1	24/07/97	AU 1437197 A	11/08/97
		CA 2241567 A	24/07/97
		CZ 9802204 A	11/11/98
		EP 0876379 A	11/11/98
		JP 10508881 T	02/09/98
		NO 983286 A	16/09/98
US 3641017 A	08/02/72	US 3733409 A	15/05/73